ON SUBSTITUTES FOR DIGITALIS.

I.—CAFFEINE.

II.—CONVALLARIA MAJALIS.

BY

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I.—Caffeine.

The alkaloid *caffeine* has been known to the profession for a number of years as an agent possessing more or less cardiac tonic powers. Neither it or any of its salts have come into anything like general use, however. This appears to be owing more to the very general trustworthy effects obtainable from digitalis, than from any positive knowledge that caffeine is not a powerful cardiac stimulant. The excellent results obtainable from the judicious use of digitalis in cases of heart failure were fully set forth by the writer in a lecture published in the December number of this Journal.

In the present article, it is proposed to describe the physiological action and uses of caffeine, and to compare it with digitalis. The salts of caffeine hitherto in use—the citrate and the hydrobromate—are unstable combinations, and, therefore, not to be relied on. The alkaloid itself is, on the other hand, so insoluble that it is not well adapted for therapeutic purposes. This unsuitability of the preparations hitherto in use for therapeutic purposes is another reason why this drug has not been more generally employed. Recently there have been introduced a number of new caffeine salts which appear to possess all the

advantages, with none of the disadvantages, of the alkaloid. Tanret has recently shown that caffeine is very soluble in aqueous solutions of the benzoate, cinnamate and salicylate of sodium. The first dissolves it in chemically equivalent quantities, so that the natro-benzoate of caffeine will contain 50 per cent. of caffeine. The natro-cinnamate and the natro-salicylate of caffeine each contain as much as 62.5 per cent. of caffeine. All three salts dissolve in two parts of hot water, and they remain in solution after the water cools. This discovery of Tanret's has given a decided impetus to the employment of caffeine, and already we have the published results of a number of accurate observations made with them in cases of heart failure. By far the most important observations made in the pharmacology and therapeutics of these salts is that of Prof. Riegel of Giessen. The great advantage of Tanret's salts is their stability and easy solubility. They can also be used hypodermically without giving rise to any but the slightest irritation.

Pharmacology of Caffeine.—The action of this drug on the heart is, in many respects, similar to digitalis, except that it has a more powerful action in influencing the circulation of healthy persons than the latter drug. That digitalis has very little influence in slowing the heart or raising the blood-pressure in a normal condition of the circulation is a matter of almost every day observation. Prof. Riegel has recently published the results of several experimental investigations that he made on six healthy young adults, with the view of determining what, if any, influence caffeine had on the normal circulation. In all these experiments the drug (the natro-salicylate) was administered hypodermically, in doses of 0.50 (7½ grains). In every case he found—1st, That the action of the heart was slightly slowed. 2nd, There was increase in the tension of the pulse. These effects were manifested half an hour after the injection, and lasted several hours. The slowing of the pulse generally amounted to about 10 beats per minute.

The fact, however, that caffeine has a considerable effect on the healthy circulation, does not necessarily imply that its effects on a diseased heart would be more pronounced than that of a

drug which has little or no influence in a healthy state of the circulatory organs. If we compare the action of caffeine with that of digitalis in pathological states, we shall find that the action of the latter is more marked than that of the former. The only remaining action of caffeine that lends importance to its usefulness as a cardiac therapeutic agent is its power of increasing the quantity of urine. It has *marked* diuretic powers. It acts as a diuretic, first, because it increases the blood-pressure when this is lowered; and, secondly, it has a directly stimulating action on the secreting structures of the kidneys.

It is in their actions on the kidneys that digitalis and caffeine differ so much from each other. The former acts solely as a diuretic owing to its power of influencing the blood-pressure, while the latter, in addition to this action, increases the secreting powers. When digitalis is administered to a patient with cardiac dropsy, it usually takes three, or it may be four, days before its diuretic powers are made manifest. Caffeine, on the other hand, increases the secretion of urine in a few hours. The cause of the slow diuretic action of digitalis is due to the fact that its primary action is first to increase the pressure throughout the whole arterial system, including that of the kidney arterioles, and it is not until the dilatation of the latter takes place that the urine commences to be excreted in greater abundance. To hurry the diuretic effects of digitalis, it has been proposed, when giving it in cases requiring a quick effect, to combine it with some drug that has the power of preventing the blood-pressure in the kidneys from being raised, while, at the same time, no influence would be exerted on the pressure in the arteries of other areas. Sodium nitrite has been suggested by Lauder Brunton as a drug likely to fulfil this purpose. Whether this suggestion will ever become of practical utility remains to be seen.

Given a case of asystolie from organic disease, we can rely on digitalis always (except in the very advanced cases of fibro-fatty degeneration) of doing good; but then we have often to wait three days before these results are obtained. Now, it is claimed for the new caffeine salts that they act with great

rapidity ; that, in the majority of cases, inside of six hours, they relieve the distressing subjective symptoms of cardio-paresis.

The following case, reported by Riegel, illustrates the usual action, according to him, of Tanret's salts of caffeine, when given in doses of about 20 grains in the 24 hours, in cases of heart-failure :—

The patient, a man aged 50, was admitted into hospital suffering from great breathlessness and œdema. There was physical evidence that the cause of these symptoms was regurgitation through the bicuspid and tricuspid orifices. The pulse was 120, and irregular ; the urine contained albumen, its specific gravity was 1018, and its quantity did not exceed 300 c.cm. in the 24 hours. After a two days' rest, without any perceptible difference in his state, he was ordered 1.00 (15 grains) of the natro-benzoate of caffeine in the 24 hours. On the following day the urine had increased to 600 c.cm., and the patient expressed himself as feeling somewhat relieved. For the following day he was ordered 1.5 (23 grains) of the same salt, with the effect that the urine had increased to 2200 c.cm., and the pulse had fallen to 88 and ceased to be irregular. The patient could now sleep in the recumbent position, which previously he was quite unable to do. The drug was then intermitted for a few days, with the result that the pulse rose to 116, the urine fell to 850 c.cm., and he was again compelled to sit up in bed. The same salt was again ordered, in the same dose, and on the day following the urine excreted amounted to 3000 c.cm. The pulse fell from 116 to 98. The discontinuance of the drug for a second time was followed by quickness and weakness of the pulse, increase of the dyspnœa, and other subjective symptoms. The quantity of urine fell to 850 c.cm. The natro-cinnamate of caffeine was now administered in place of the natro-benzoate, and with very satisfactory results. The pulse fell from 108 to 88 within the first 24 hours, and the quantity of urine increased from 850 to 2000 c.cm. The patient expressed himself as feeling once more greatly relieved.

The most pronounced action of the caffeine salts in the case related was (1st) a very considerable increase in the quantity

of urine, and (2nd) a slowing and steadying of the heart's movements. Prof. Riegel reports a number of very similar cases, where the results were invariably very satisfactory. In only one instance did it fail to produce the wished-for effect, and that was in a case where it was combined with morphia. A subsequent administration without the latter drug was followed by an increase in the quantity of the urine and a slowing of the pulse. Binz has pointed out that there exists a marked antagonism between caffeine and narcotics, especially morphia. It is difficult to explain how this alleged antagonism is brought about. It is, however, well to remember the possibility of its occurrence when prescribing caffeine. It is extremely seldom that the occasion can arise for the administration of morphia or other direct narcotic to combat the sleeplessness frequently present, and due to a failing heart. The best treatment for this form of insomnia is not a narcotic, but a cardiac stimulant like caffeine or digitalis. In other words, the sleeplessness due to ruptured compensation is best treated by an agent that restores the compensation to its previous state. When using caffeine especially, it is unnecessary to prescribe a direct hypnotic, seeing that in a few hours one may attain a better and more permanent result, because we remove the cause of the trouble.

The actions and uses of caffeine, when used in the form of the recently-introduced double salts may be summed up as follows :

1. It strengthens, slows, and steadies a weak, fast and irregular heart.

2. It quickly acts as a diuretic in cardiac dropsy, owing to its power of (*a*) raising the blood-pressure and (*b*) of stimulating the secreting structures of the kidneys.

3. It is of marked use in the same class of cases as digitalis is. It differs, however, from this drug in the following particulars : (*a*) It is less powerful as a cardiac tonic ; (*b*) It is a more powerful and prompt diuretic, and for this reason it gives relief quicker from all the troublesome subjective symptoms of cardiac failure.

It is probable that results obtainable from neither of these drugs when given singly, could be brought about if caffeine was

given first and its effects kept up until the cumulative action of digitalis could be made manifest. By combining the power of digitalis with the rapidity of action of caffeine we may get the advantages of both drugs with little of the disadvantages of either. There is no published evidence relating to these points, however.

Dose and mode of administration of Caffeine.—The dose of any of the double salts should not exceed 30 grains in the 24 hours, this quantity being equal to about 20 grains of the pure alkaloid. Usually half the above dose will answer all purposes. The double salts are prepared by Merck of Darmstadt, but have not, as yet, found their way to this side of the Atlantic. They, however, can be prepared extemporaneously. The following formula contains in each tablespoonful about 1.00 (15 grains) of caffeine :—

℞ Caffeine - - - 15.00 (gr. 225)
Benzoate of Soda, 15.00 (gr. 225)
Water, - - - 250.00 (℥viij)

The doses of caffeine (2 or 3 grains) usually ordered are quite inadequate to act either as diuretics or cardiac tonics.

II.—Convallaria Majalis.

During the few years that have elapsed since the lily of the valley has been recommended as a substitute for digitalis, extensive trials have been made with it, especially in the French and German clinics. There is far from being anything like a general consensus of opinion as to its capabilities, when used for the above purpose. Some consider it to be equal, if not superior, to digitalis, while others say that it is entirely untrustworthy.

In the present article an attempt will be made to present the pharmacology and therapeutics of this agent, according to the more recent researches into its actions and uses

It was first introduced to the notice of the profession about three years ago by Botkin, the celebrated Russian physician.

It is, however, a very old remedy, being mentioned even by Dioscorides, who considered it very beneficial in palpitations; "*it fortifyes the heart*," he says.

Botkin was led to employ it owing to its popularity as an "anti-dropsical" remedy among the Russian peasantry.

He alleges that he has always found it a reliable cardiac tonic, even in some cases surpassing digitalis. German Sée considers that in many cases it is the equal, and in a few cases the superior, of digitalis. Leyden, Lubinski, Fränkel, Stiller and others maintain, on the other hand, that in all cases it is inferior to digitalis; and in many cases, they say, it entirely fails to strengthen a weak heart.

At least, a part of this marked discrepancy of opinion is clearly due to the fact, that the various experimenters referred to employed preparations of different strengths, and made from different parts of the plant. Some used an extract (watery or alcoholic) from the flowers, while others used an infusion of the whole plant.

The strength of convallaria preparations depends much on their place of growth and the time the plant is collected. Russian plants are said to be superior, while American are inferior to all others. The flowers contain in greatest abundance the glucoside convallamarin, to which the plant owes all its medicinal properties,—at least its cardiac properties—for, in addition, there is another glucoside, which has been called convallaria, which possesses marked intestinal irritant properties, but is destitute of any cardiac tonic powers.

Pharmacology.—When applied to the heart of a frog, the different preparations of convallaria have a distinct tonic action. They slow and render the heart's movements more powerful. A similar action is observed in warm-blooded animals, although not so marked. Sphygmographic tracings taken from the pulse of man, after a few doses of convallaria, show that not only is the number of pulsations diminished, but the amplitude of the contractions is increased.

If administered in over-doses to either cold or warm-blooded animals, it brings the heart to a systolic arrest.

Through what agencies it slows and strengthens the heart's movements and increases the blood pressure, has not been definitely determined.

It is claimed by German Sée and other French observers that it has marked diuretic powers. That in addition to its power increasing the quantity of urine through its action on the blood pressure, it has a direct influence in stimulating the secreting structures of the kidneys. The diuretic action of convallaria resembles that of caffeine. It has no influence, it is said, in causing any considerable increase in the quantity of urine in a normal condition of the circulation. It is eliminated for the most part by the kidneys, and on heating the urine of a patient who has been taking it for a few days, a slight cloudiness is observable, due to the resin of the plant and not to albumen.

Therapeutics.—The only use of convallaria is as a heart tonic, in cases of failure due to organic disease. It is said to be especially operative in cases of dropsy due to mitral lesions. Its power in strengthening a failing heart is much less than that of digitalis. The latter drug, except in advanced cases of fibro-fatty degeneration, if properly administered, seldom or never fails of at least partially restoring a ruptured compensation.

Convallaria, at times, acts as well as digitalis, and frequently with more promptitude, but in a considerable number of cases it is much less efficient—while it not unfrequently fails entirely in bringing about the wished for results.

If the three prominent cardiac tonics were to be arranged in the order of their power, we would have digitalis first, caffeine next, and convallaria occupying the third place. Arranged according to the promptitude of their action, caffeine would be the first on the list, convallaria second and digitalis third. Arranged according to the order of their freedom from untoward effects, caffeine would certainly hold the first place, convallaria the second and digitalis the third. A preparation made from all parts of the convallaria plant is as likely to cause gastric disturbance as digitalis, while it is much more likely to cause intestinal irritation than the latter. Preparations of the leaves and of the glucoside convallamarin are, however, seldom, if ever, fol-

lowed by any intestinal irritation. The reason that preparations of the whole plant are more apt to cause diarrhœa and vomiting, is that the root contains nearly all the convallaria,—the glucoside—whose actions are entirely those of a gastro-intestinal irritant.

The two following cases may be taken as representing the most favorable action of convallaria in organic disease of the heart. The first is reported by Falkenheim* from the clinic of Prof. Naunyn, of Königsberg. The patient was a woman, aged forty-three. When admitted into hospital she was found to have stenosis with insufficiency of the mitral orifice. There were extensive secondary changes in the heart, together with advanced atrophic nutmeg liver. There was great effusion into the abdomen, as well as into the subcutaneous cellular tissue. The pulse was 90, and the quantity of urine in the twenty-four hours did not exceed 500 c.c. (15 oz.) Two days after the administration of an infusion of the flowers, the pulse gradually began to fall and the urine to increase in quantity. So marked was the increase of urine that the patient was passing 3000 c.cm. ten days after the commencement of the treatment. The pulse fell from 90 to 50. The patient was discharged shortly afterwards, much improved. She was, however, after a few weeks, readmitted in a very similar state to what she was when she first came under observation. The quantity of urine was no more than 500 c.cm. in the twenty-four hours, and her pulse was 90. An infusion of the convallaria leaves was again ordered, with the result that the urine in a day or two commenced to increase in quantity. This increase was gradually augmenting during the ten days that the drug was given, when it reached 2500 c.cm. in the twenty-four hours. At the time that the quantity of urine passed in the twenty-four hours had reached its highest point, the patient had also diarrhœa. The pulse fell from 90 to 60. Coupled with the increased quantity of urine and the fall in the pulse rate, there was a marked relief in all the distressing subjective symptoms which troubled her.

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It should be mentioned that just before the patient was admitted the first time into the hospital, she had been tapped.

The second case* is one reported by Dr. F. T. Roberts, of University College. It was one of mitral obstructive disease, with irregular and inefficient cardiac action; deficient secretion of urine; moderate dropsy of the legs and considerable ascites. The obvious results of the administration of the convallaria were:

1. A distinct improvement in the action of the heart, which became more regular and efficient, while the thrill and murmur became more evident.

2. A considerable and progressive increase in the quantity of urine produced.

3. Rapid diminution and ultimate disappearance of the œdema of the legs and the ascites.

In speaking of this case, Dr. Roberts says "that the compound jalap powder helped, no doubt, to get rid of the last symptoms; but the other effects noted were, unquestionably, due to the convallaria, and the increase in the quantity of urine must have been an important factor in removing the dropsical accumulation. I have thought it worth while to report this case in support of the value of convallaria in the treatment of cardiac affections, although I do not for a moment believe that it will entirely supersede other drugs. The patient is now practically well, so far as symptoms is concerned, but the signs of mitral obstructive disease are very distinct."

Dose and Mode of Administration.—Judging from a few trials, the glucoside convallamarin possesses all the active cardiac properties of the plant, with none of its disadvantages. Preparations made from the plant itself are much more likely to bring about vomiting and diarrhœa. For these reasons, the convallamarin should be preferred. Next to it, as an efficient preparation is a fluid extract of the flowers. An infusion of the whole plant is not only unreliable, but is very apt to disagree.

The dose of convallamarin is from one to two grains. It can be made into pill with glycerine of tragacanth.

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* *Practitioner*, April, 1884.